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10/581,538	04/12/2007	Shawn DeFrees	705711	6190

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EXAMINER
GOON, SCARLETT Y

ART UNIT	PAPER NUMBER
1623	

NOTIFICATION DATE	DELIVERY MODE
12/17/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/581,538	DEFREES ET AL.	
	Examiner	Art Unit	
	SCARLETT GOON	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 September 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *6 and 13-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-12 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2 June 2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-23 are pending in the instant application.

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-12 and 23, drawn to a follicle stimulating hormone peptide conjugate, in the reply filed on 17 September 2009 is acknowledged. Applicants further elect the formula for R^1-L- as denoted in claim 2, and branched poly(ethylene glycol), in response to the requirement for an election of a single disclosed species. The traversal is on the ground(s) that the restriction is improper because unity of invention exists across the claims of Groups I-III since the claims are all drawn to "(3) A product, a process specially adapted for the manufacture of the said product, and a use of the said product..." This is not found persuasive because, according to PCT Rule 13.1, and as indicated in the Requirement for Restriction dated 17 August 2009, unity of invention exists only when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding special technical features. The expression “special technical features” is defined in PCT Rule 13.2 as meaning those technical features that define a contribution which each of the inventions, considered as a whole, makes over the prior art. As indicated in Requirement for Restriction, the common technical feature in all groups is a follicle stimulating hormone peptide comprising the structure having the formula as shown in instant claim 1. However, WIPO publication WO 03/031464 A2 to DeFrees *et al.* discloses such a conjugate. As a result, no special technical features

exist among the different groups because the inventions in Groups I-III fail to make a contribution over the prior art with respect to novelty and inventive step. In conclusion, there is a lack of unity of inventions, and therefore restriction for examination purposes as indicated is proper.

The requirement is still deemed proper and is therefore made FINAL.

Claims 13-22 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 17 September 2009.

Claim 6 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 17 September 2009.

Claims 1-5, 7-12 and 23 will be examined on its merits herein.

Information Disclosure Statement

The information disclosure statement (IDS) dated 2 June 2006 complies with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609. Accordingly, it has been placed in the application file and the information therein has been considered as to the merits.

Priority

This application is a National Stage entry of PCT/US04/40709 filed on 3 December 2004 and claims priority to U.S. provisional application no. 60/527,082 filed on 3 December 2003, U.S. provisional application no. 60/539,387 filed on 26 January 2004, U.S. provisional application no. 60/592,744 filed on 29 July 2004, U.S. provisional application no. 60/614,518 filed on 29 September 2004 and U.S. provisional application no. 60/623,387 filed on 29 October 2004.

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir 1994). Also see MPEP § 201.11.

The disclosure of the prior-filed applications, U.S. provisional application no. 60/527,082 filed on 3 December 2003, U.S. provisional application no. 60/539,387 filed on 26 January 2004, U.S. provisional application no. 60/592,744 filed on 29 July 2004, U.S. provisional application no. 60/614,518 filed on 29 September 2004 and U.S.

provisional application no. 60/623,387 filed on 29 October 2004, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. The prior filed applications, U.S. provisional application no. 60/527,082 and U.S. provisional application no. 60/539,387, do not disclose a conjugate comprising a branched PEG comprising serine, cysteine, or lysine as the linkers. The prior filed applications, U.S. provisional application no. 60/592,744, U.S. provisional application no. 60/614,518, and U.S. provisional application no. 60/623,387, do not disclose the genus of branched polymers as recited in instant claims 3-5. Specifically, the prior filed applications do not disclose varying the carbon chain length, designated as variable "q" in the instant claims.

Thus, the priority date of the instant claims **3-5** is deemed to be the filing date of the only application that provides support for the claimed subject matter, that being the instantly filed application filed on 12 April 2007. If Applicants disagree, Applicants should present a detailed analysis as to why the claimed subject matter has clear support in the earlier priority applications. Applicant is reminded that such priority for the instant limitations requires written description and enablement under 35 U.S.C. § 112, first paragraph.

In clarifying the priority date of the instant claims, applicant should note or address whether the art rejections are prior to the priority date of the instant claims and whether said art occurred more than one year prior to said priority date.

Specification

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below:

The application does not contain disclosures of nucleotide and/or amino acid sequences for SEQ ID No. 1 and 2. Moreover, disclosures of SEQ ID No. 1 and 2 must be submitted as a separate part of the disclosure, a paper or compact disc copy (see § 1.52(e)) disclosing the nucleotide and/or amino acid sequences and associated information using the symbols and format in accordance with the requirements of §§ 1.822 and 1.823.

In an effort to expedite prosecution, SEQ ID No. 1 and 2 has been interpreted as being the human FSH sequences for the α- and β-subunits, respectively, as disclosed in PG Pub No. US 2003/0166525 A1 to Hoffman *et al.* (PTO-892, Ref. A), since the sites of glycosylation for the human FSH sequence matches that of the instant claims, thereby suggesting they are the same sequence.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 9 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The formula of claim 9 indicates that "r, s, t and u are integers independently selected from 0 and 1." This recitation renders the claim herein indefinite because when r, s, t and u all have an integer of 0, the glycosyl moiety no longer contains a sialic acid residue, much less a modified sialic acid residue, and would therefore not meet the limitation of parent claim 1, which requires that at least one of the conjugate moieties have a modified sialic acid residue.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1, 2, 7-12 and 23 are rejected under 35 U.S.C. 102(a) and 35 U.S.C. 102(e) as being anticipated by WIPO publication WO 03/031464 A2 to DeFrees *et al.* (please see PG Pub No. US 2007/0042458 A1 for equivalent; of record), as evidenced by journal publication by Ulloa-Aguirre *et al.* (PTO-892, Ref. V), and as evidenced by PG Pub No. US 2003/0166525 A1 to Hoffman *et al.* (PTO-892, Ref. A).

DeFrees *et al.* disclose methods and compositions for remodeling a peptide molecule, including the addition or deletion of one or more glycosyl groups to the peptide, and/or the addition of a modifying group to the peptide. Modifying groups include water-soluble polymers, such as poly(ethylene glycol) (p. 152, lines 7-25 of WIPO; paragraphs 0655-0657 of PG Pub). The use of poly(ethylene glycol) to derivatize peptide therapeutics has been demonstrated to reduce the immunogenicity of the peptides and prolong their clearance time from circulation (paragraph 0011 of PG Pub). The PEG moiety has been shown to be attached via a peptide amino acid residue (paragraph 0013 of PG Pub) or an oxidized glycosyl residue of the peptide (paragraph 0014 of PG Pub). DeFrees *et al.* disclose an *in vitro* method for the modification of erythropoietin (EPO), wherein the peptide has the formula –AA-X^1-X^2 (paragraph 0031 of PG Pub) or formula –AA-$(X^1)_n$. More specific structures of the X^1-X^2 glycosyl residues are shown in paragraph [0067], paragraph [0082], paragraph [0088], paragraph [0090] and paragraph [0114]. Scheme 3 discloses a modified glycoPEG-ylated compound, such as albumin-PEG-SA-EPO, wherein EPO represents erythropoietin and SA represents sialic acid, which can be used in a method for extending the blood-circulation half-life of selected peptide (p. 149, Scheme 3 and lines 1-10 of WIPO; paragraph 0643 of PG Pub). Additionally, Example 23 discloses a method for glycoPEGylation of human pituitary-derived follicle stimulating hormone (FSH) (paragraphs 1567-1573) and Example 24 discloses a method for the glycoPEGylation of recombinant FSH produced recombinantly in CHO cells (paragraphs 1574-1579). The methods are further schematically represented in Figure 34 which

discloses the modification of the glycan structure on follicle stimulating hormone with PEG (paragraph 0219 of PG Pub). The modifying group can be attached to sialic acid occurs at either the 9-position on the pyruvyl side chain or at the 5-position on the amine moiety of sialic acid (p. 150, lines 5-11 of WIPO; paragraph 0647 of PG Pub). DeFrees *et al.* further teach that the reactive functional groups between the sugar moiety and the modifying group can include such functional groups as amines and carboxyl groups (paragraphs 0753. 0754, and 0760 of PG Pub).

It is noted that DeFrees *et al.* do not expressly disclose the site of glycoPEGylation on the peptide backbone, or the sequence FSH. However, as evidenced by Hoffmann *et al.*, human FSH has the sequence as disclosed in Seq. ID No. 5 and Seq. ID No. 6 (columns 39 and 40), corresponding to the α- and β-subunits, respectively. Applicants are requested to note that their instantly claimed SEQ ID No. 1 and 2 are non-compliant as the sequences were not submitted with the application. In the absence of any additional information provided in the Specification with regards to the specific sequences of SEQ ID No. 1 and 2 as recited in claim 8, SEQ ID No. 1 and 2 is considered to have the same sequence as Seq. ID No. 5 and 6, respectively, as disclosed by Hoffmann *et al.* Therefore, since DeFrees *et al.* teach that the FSH used in their method was derived from a human, it is expected that it would have the same sequence as that disclosed by Hoffmann *et al.* With regards to the site of glycosylation, as evidenced by Ulloa-Aguirre *et al.*, N-glycosylation of FSH occurs at positions N52 and N78 of the α-subunit, and at positions N7 and N24 of the β-subunit. Therefore, it is

inherent that the PEGylated glycosyl residue would be present only at these four asparagine sites.

Thus, the disclosure of a glycoPEGylated FSH, as well as a method for the preparation of said structure, disclosed by DeFrees *et al.*, anticipates claims 1, 2, 7-12 and 23.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Section [0001]

Claims 3-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over WIPO publication WO 03/031464 A2 to DeFrees *et al.* (please see PG Pub No. US 2007/0042458 A1 for equivalent; of record), as evidenced by journal publication by Ulloa-Aguirre *et al.* (PTO-892, Ref. V), and as evidenced by PG Pub No. US 2003/0166525 A1 to Hoffman *et al.* (PTO-892, Ref. A), as applied to claims 1, 2, 7-12 and 23, further in view of U.S. Patent No. 5,643,575 to Martinez *et al.* (hereinafter referred to as the '575 patent; PTO-892, Ref. B) and journal publication by Felix *et al.* (PTO-892, Ref. W).

The teachings of DeFrees *et al.* were as disclosed above in the claim rejections made under 35 USC § 102. The evidentiary disclosure of Gervais *et al.*, Ulloa-Aguirre *et al.*, and Hoffman *et al.*, were as disclosed above in the claim rejections made under 35 USC § 102.

The Martinez '575 patent teaches branched, non-antigenic polymers and conjugation of the polymers to biologically active molecules such as proteins and peptides as a means to extend their circulating half-life *in vivo*. One of the chief advantages for the use of branching polymers is that the branching polymers impart an umbrella-like three-dimensional protective covering to the materials they are conjugated

with (column 2, lines 42-51). Another advantage is that the branched polymers provide the benefits associated with attaching several strands of polymers to a bioeffecting material, but require substantially fewer conjugation sites, which is apparent in therapeutic agents having few available attachment sites (column 2, lines 52-59). The branched polymers are represented by formula (I), $(R)_nL$-A, wherein R is the water-soluble polymer, n is 2 or 3, L is the aliphatic linking moiety covalently lined to R, and A represents the activating functional group (column 3, lines 11-22). The polymers are preferably prepared from methoxypoly (ethylene glycols), or other suitable alkyl substituted poly(alkylene oxide) derivative, such as those containing mono or bis terminal C_1-C_4 groups (column 2, lines 65 - column 3, line 4). Straight-chained non-antigenic polymers such as monomethyl PEG (mPEG) homopolymers are preferred (column 3, lines 4-6). It is preferred that each mPEG chain have a molecular weight of between 200 and about 12,000 Da, with molecular weights of about 5,000 Da being most preferred (column 3, lines 23-29). The variable L preferably includes a multiply-functionalized alkyl group containing up to 13, and more preferably, between 1-10 carbon atoms (column 3, lines 59-63). A heteroatom, such as nitrogen, oxygen or sulfur may be included within the alkyl chain, which may also be branched at a carbon or nitrogen atom. The variable “A” is selected from any functional group that is capable of reacting with 1) an amino group, 2) a carboxylic acid group or reactive carbonyl group, or 3) mercapto or sulfhydryl groups. The variable “A” can also include a spacer moiety located proximal to the aliphatic linking moiety “L” (column 4, lines 47-50). Biologically active molecules of interest include, but are not limited to, proteins, peptides,

polypeptides, enzymes, organic molecules of natural and synthetic origin such as medicinal chemicals, and the like (column 7, lines 40-45). Among the list of proteins cited as being of interest is follicle-stimulating hormone (column 8, line 5). Example 8 discloses the preparation of a branched PEG structure wherein lysine is the linker conjugated to two linear mPEG compounds (column 13, lines 20-40).

Felix *et al.* teach the synthesis of symmetrically and asymmetrically branched pegylating reagents. PEG-protein conjugates have been shown to have improved bioavailability and therapeutic efficacy stemming from increased resistance to proteolytic degradation, enhanced pharmacokinetic and improved pharmacodynamic properties, and reduced renal clearance (p. 86, column 1, first paragraph). Additionally, many pegylated proteins have been reported to have increased plasma half-lives and reduced antigenicity and immunogenicity (p. 86, column 1, first paragraph). Branched PEGS offer an additional dimension of steric protection to the proteins to which they are linked (p. 86, column 2, bridging paragraph). Lysine has been used successfully as a spacer for branched PEG structures (p. 86, column 1, last paragraph). It is expected that introduction of additional branches to PEG would provide additional levels of enzymatic protection to the proteins to which they are linked (p. 86, column 2, first full paragraph). Felix *et al.* disclose a branched bis-pegylating reagent wherein lysine is used as the linker, and a tris-pegylating reagent wherein glutamate-lysine is used as the linker (p. 87, column 1, Figure 1). Methods for the preparation of the bis-pegylating reagent and tris-pegylating reagent are disclosed in Figure 2 (p. 87).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of DeFrees *et al.*, concerning a glycoPEGylated FSH, with the teachings of the Martinez '575 patent, regarding the use of branched, non-antigenic PEG polymers and conjugation of these PEG polymers to biologically active molecules such as proteins and peptides as a means to extend their circulating half-life *in vivo*, with the teachings of Felix *et al.*, regarding a bis-pegylating reagent and a tris-pegylating reagent based on amino acids, such as lysine and glutamate-lysine, as the backbone linker. Since both the Martinez '575 patent and Felix *et al.* teach that one of the chief advantages for the use of branched polymers is that the branching polymers impart an umbrella-like three-dimensional protective covering to the materials they are conjugated with, one of ordinary skill in the art would have been motivated to substitute the linear PEG polymers of PEGylated FSH with the branched polymers disclosed in either the Martinez '575 patent or by Felix *et al.*, in order to receive the expected benefit that the resulting branched PEGylated FSH would exhibit greater protection with regards to proteolytic cleavage and serum half-life.

Furthermore, since the Martinez '575 patent teaches that branched PEG polymers can be synthesized by using any linker that comprises a multiply-functionalized alkyl group containing up to 13 carbons, further exemplifying lysine as such a linker, and Felix *et al.* teach that lysine and glutamate, individually, or combined, can be used as the linker for generating branched PEG polymers, one of ordinary skill in the art would have been motivated to combine the teachings and arrive at the conclusion that different amino acids could likewise be used as the linker for generation

of branched PEG polymers. Since lysine and glutamate are both amino acids, and many of the natural amino acids, such as cysteine and serine, meet the limitations of being a linker as defined in the Martinez '575 patent, one of ordinary skill in the art would have been motivated to substitute the lysine linker backbone as disclosed in the Martinez '575 patent with other amino acids, such as serine or cysteine, with the expectation that such a substitution would similarly generate useful branched PEG polymers. Moreover, since Felix *et al.* teach that a tris-pegylating reagent can be generated based on a glutamate-lysine backbone, it would have been *prima facie* obvious for one of ordinary skill to substitute glutamate with another amino acid, such as a lysine residue, to form a lysine-lysine backbone, with the expectation that such a substitution would similarly generate useful tri-branched PEG polymers.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Section [0002]

Claims 1, 2, 7, 9, 10, 12 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over WIPO publication WO 94/05332 to M'Timkulu (IDS dated 2 June 2006), in view of U.S. Patent No. 6,586,398 B1 to Kinstler *et al.* (hereinafter referred to as the '398 patent, PTO-892, Ref. C) and U.S. Patent No. 5,643,575 to Martinez *et al.* (hereinafter referred to as the '575 patent; PTO-892, Ref. B), as evidenced by Gervais *et al.* (PTO-892, Ref. U), as evidenced by journal publication to Ulloa-Aguirre *et al.*

(PTO-892, Ref. V), and as evidenced by journal publication to Kawasaki *et al.* (PTO-892, Ref. X).

M'Timkulu teaches a process for coupling glycols to macromolecules through the glycosylations on those macromolecules, instead of through the amino or carboxyl groups on the macromolecule backbone itself (p. 5, lines 18-22). The resulting conjugates are used in a method for reducing the immunogenicity of biologically active macromolecules, while maintaining their activity (p. 5, lines 12-14). The conjugates also exhibit increased biological half-life due to steric blocking of clearance receptors, increased solubility of hydrophobic molecules in an aqueous environment due to the addition of lipophilic moities, and an increased resistance to proteolysis due to steric hindrance (p. 5, lines 22-30). Macromolecules useful in the disclosed process include virtually any bioactive macromolecule bearing glycosylations, or which can be glycosylated, e.g., polypeptides and/or proteins, nucleic acids, lipids, or carbohydrates (p. 6, lines 26-30). Preferred peptides include those comprising an antigen binding region, a cytokine, a receptor, an antithrombotic, a growth factor, or an angiohypotensive reagent (p. 6, lines 31-33). The disclosed procedures are also applicable to peptide hormones, such as insulin and luteinizing hormone, among others (p. 7, lines 10-12 and 28-34). The glycol is preferably polyethylene glycol, especially mono-methoxyethylene glycol with a repeating glycol unit between 2-500 (p. 8, lines 9-15) and a molecular weight of up to 24,000 (p. 6, lines 17-21). The glycol is conjugated to the macromolecule via one of the glycosylation residues present on the macromolecule, such as galactose, mannose, glucose, N-acetylglucosamine, N-

acetylgalactosamine, sialic acid, fucose, and/or xylose (p. 8, lines 1-8). The pegylation of monoclonal antibody Tab-250 through its carbohydrate moieties is exemplified (p. 13-15). The carbohydrate moiety is first oxidized with sodium periodate, prior to conjugation with PEG (p. 9, lines 15-35; p. 14, lines 4-22).

The teachings of M'Timkulu differ from that of the instantly claimed invention in that M'Timkulu do not disclose the specific position on the carbohydrate residue of the macromolecule that is being conjugated to PEG. Furthermore, while M'Timkulu discloses that their disclosed conjugation methods are useful for peptide hormones, M'Timkulu does not disclose follicle stimulating hormone as one such peptide hormone.

The Kinstler '398 patent teaches the attachment of water soluble polymers to a hyperglycosylated erythropoietin analog (NESP) having five changes in the amino acid sequence of rHuEPO to provide for two additional N-linked carbohydrate chains. Pharmaceutical compositions comprising PEGylated NESP exhibit a dramatic sustained duration profile as compared to non-PEGylated NESP (column 2, lines 22-29). Several methods are provided for the preparation of PEG conjugated to NESP (column 5, lines 1-6). One method involves the mild oxidation of NESP under conditions selected to target the pendant diol of the penultimate glycosyl unit sialic acid for oxidation to an aldehyde (column 5, lines 25-32). The resultant glycoaldehyde is then reacted with methoxy-PEG-hydrazide to form a semi-stable hydrazone between PEG and NESP. Example 1 illustrates the conjugation of PEG with NESP through aldehydes generated in the NESP carbohydrate chains by sodium periodate oxidation of the terminal sialic acid residues (column 9, lines 20-38). Table 1 (column 11) shows that both linear and

branched forms of PEG can be conjugated to the sialic acid residue of NESP. The Kinstler '398 patent further teaches that PEG conjugated to NESP can be formulated into pharmaceutical compositions comprising effective amounts of protein or derivative products together with pharmaceutically acceptable diluents, stabilizers, preservatives, solubilizers, emulsifiers, adjuvants and/or carriers (column 7, lines 46-50).

The teachings of the Martinez '575 patent were as disclosed above in section [0001] of the claim rejections made under 35 USC § 103.

It is noted that the prior art references do not explicitly teach that the modified glycosyl moiety has the structure as shown in instant claim 9. However, as evidenced by Gervais *et al.*, FSH is glycosylated with the same glycosyl structure as shown in instant claim 9 (p. 181, Figure 3A, peak at about 49 min).

It is further noted that the prior art references do not explicitly teach that PEGylation occurs on the glycosyl residues attached to the peptide via an asparagine residue. However, as evidenced by Ulloa-Aguirre *et al.*, human FSH glycosyl modification occurs via N-linked glycosylation to the asparagine residue of the peptide backbone (p. 205, column 2).

As such, it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of M'Timkulu, concerning the conjugation of PEG polymers to biologically active macromolecules through the glycosylations present on those macromolecules, with the teachings of the Kinstler '398 patent, regarding the attachment of PEG polymers to the sialic acid residue of EPO as a means to alter their serum half-life, with the teachings of the Martinez '575 patent, regarding the conjugation

of branched, non-antigenic PEG polymers to biologically active molecules, such as proteins and peptides, as a means to extend their circulating half-life *in vivo*.

Since M'Timkulu teach that biological macromolecules, such as hormone peptides, can be conjugated to PEG polymers through the glycosylations present on those macromolecules, as a means to reduce the immunogenicity of biologically active macromolecules, while maintaining their activity, and the Martinez '575 patent teaches that branched, non-antigenic polymers can be conjugated to biologically active molecules, such as FSH, as a means to extend their circulating half-life *in vivo*, it would have been *prima facie* obvious for one of ordinary skill in the art to conjugate PEG to FSH using the conjugation method as described by M'Timkulu. Since both M'Timkulu and the Martinez '575 patent teach conjugation of PEG to biological macromolecules as a means to extend their serum half-life, and M'Timkulu further teaches that hormones can be conjugated using their disclosed method, one of ordinary skill in the art would reasonably expect that the use of follicle stimulating hormone, as disclosed in the Martinez '575 patent, for conjugation to a PEG polymer using the method disclosed by M'Timkulu, would result in PEGylation of FSH at the glycosyl moiety present on FSH.

With regards to the specific glycosyl residue of FSH for PEGylation, the Kinstler '398 patent teaches that EPO can be conjugated to PEG via oxidation of the glycerol side chain on the terminal sialic acid residue present on glycosylated EPO. Since the glycosyl moiety present on FSH is the same as that present on EPO, as evidenced by Gervais *et al.* and Kawasaki *et al.*, respectively, one of ordinary skill in the art would

have a reasonable expectation of success in PEGylating FSH via the sialic acid residue present on the FSH polypeptide backbone.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Section [0003]

Claims 3-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over over WIPO publication WO 94/05332 to M'Timkulu (IDS dated 2 June 2006), in view of U.S. Patent No. 6,586,398 B1 to Kinstler *et al.* (hereinafter referred to as the '398 patent, PTO-892, Ref. C) and U.S. Patent No. 5,643,575 to Martinez *et al.* (hereinafter referred to as the '575 patent; PTO-892, Ref. B), as evidenced by Gervais *et al.* (PTO-892, Ref. U), as evidenced by journal publication to Ulloa-Aguirre *et al.* (PTO-892, Ref. V), and as evidenced by journal publication to Kawasaki *et al.* (PTO-892, Ref. X), as applied to claims 1, 2, 7, 9, 10, 12 and 23, further in view of journal publication by Felix *et al.* (PTO-892, Ref. W).

The teachings of M'Timkulu and the Kinstler '398 patent were as disclosed in section [0002] above of the claim rejections made under 35 USC § 103. The teachings of the Martinez '575 patent were as disclosed above in section [0001] of the claim rejections made under 35 USC § 103. The evidentiary disclosures of Kawasaki *et al.*, Gervais *et al.* and Ulloa-Aguirre *et al.* were as disclosed in section [0002] above in the claim rejections made under 35 USC § 103.

The combined teachings of M'Timkulu, the Kinstler '398 patent, and the Martinez '575 patent differ from that of the instantly claimed invention in that the prior art references do not disclose the specific PEG structures as recited in the instant claims.

The teachings of Felix *et al.* were as disclosed above in section [0001] of the claim rejections made under 35 USC § 103.

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of M'Timkulu, concerning the conjugation of PEG polymers to biologically active macromolecules through the glycosylations present on those macromolecules, with the teachings of the Kinstler '398 patent, regarding the attachment of PEG polymers to the sialic acid residue of EPO as a means to alter their serum half-life, with the teachings of the Martinez '575 patent, regarding the conjugation of branched, non-antigenic PEG polymers to biologically active molecules, such as proteins and peptides, as a means to extend their circulating half-life *in vivo*, with the teachings of Felix *et al.*, regarding a bis-pegylating reagent and a tris-pegylating reagent based on amino acids as the backbone linker.

Since both the Martinez '575 patent and Felix *et al.* teach that one of the chief advantages for the use of branched polymers is that the branching polymers impart an umbrella-like three-dimensional protective covering to the materials they are conjugated with, one of ordinary skill in the art would have been motivated to substitute the linear PEG polymers on PEGylated FSH, based on the combined teachings of M'Timkulu, the Martinez '575 patent, and the Kinstler '398 patent (as disclosed in section [0002] rejection), with the branched polymers disclosed in either the Martinez '575 patent or by

Felix *et al.*, in order to receive the expected benefit that the resulting branched PEGylated FSH would exhibit greater protection with regards to proteolytic cleavage and serum half-life.

Furthermore, since the Martinez '575 patent teaches that branched PEG polymers can be synthesized by using any linker that comprises a multiply-functionalized alkyl group containing up to 13 carbons, further exemplifying lysine as such a linker, and Felix *et al.* teach that lysine and glutamate, individually, or combined, can be used as the linker for generating branched PEG polymers, one of ordinary skill in the art would have been motivated to combine the teachings and arrive at the conclusion that different amino acids could likewise be used as the linker for generation of branched PEG polymers. Since lysine and glutamate are both amino acids, and many of the natural amino acids, such as cysteine and serine, meet the limitations of being a linker as defined in the Martinez '575 patent, one of ordinary skill in the art would have been motivated to substitute the lysine linker backbone as disclosed in the Martinez '575 patent with other amino acids, such as serine or cysteine, with the expectation that such a substitution would similarly generate useful branched PEG polymers. Moreover, since Felix *et al.* teach that a tris-pegylating reagent can be generated based on a glutamate-lysine backbone, it is would have been *prima facie* obvious for one of ordinary skill to substitute glutamate with another amino acid, such as a lysine residue, to form a lysine-lysine backbone, with the expectation that such a substitution would similarly generate useful tri-branched PEG polymers.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Section [0004]

Claims 8 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over over WIPO publication WO 94/05332 to M'Timkulu (IDS dated 2 June 2006), in view of U.S. Patent No. 6,586,398 B1 to Kinstler *et al.* (hereinafter referred to as the '398 patent, PTO-892, Ref. C) and U.S. Patent No. 5,643,575 to Martinez *et al.* (hereinafter referred to as the '575 patent; PTO-892, Ref. B), as evidenced by Gervais *et al.* (PTO-892, Ref. U), as evidenced by journal publication to Ulloa-Aguirre *et al.* (PTO-892, Ref. V), and as evidenced by journal publication to Kawasaki *et al.* (PTO-892, Ref. X), as applied to claims 1, 2, 7, 9, 10, 12 and 23, further in view of PG Pub No. US 2003/0166525 A1 to Hoffman *et al.* (PTO-892, Ref. A).

The teachings of M'Timkulu and the Kinstler '398 patent were as disclosed in section [0002] above of the claim rejections made under 35 USC § 103. The teachings of the Martinez '575 patent were as disclosed above in section [0001] of the claim rejections made under 35 USC § 103. The evidentiary disclosures of Kawasaki *et al.*, Gervais *et al.* and Ulloa-Aguirre *et al.* were as disclosed in section [0002] above in the claim rejections made under 35 USC § 103.

The combined teachings of M'Timkulu, the Kinstler '398 patent, and the Martinez '575 patent differ from that of the instantly claimed invention in that the prior art

references do not disclose the specific sequence of FSH, or the site of glycoPEGylation on FSH, as recited in the instant claims.

Hoffman *et al.* teach the sequence of FSH from various origins, including the α- and β-subunits from mammalian and *homo sapiens* sources (p. 21-25). Hoffmann *et al.* teach that human FSH has the sequence as disclosed in Seq. ID No. 5 and SEQ ID No. 6 (p. 22 and 23), corresponding to the α- and β-subunits, respectively. Applicants are requested to note that their instantly claimed SEQ ID No. 1 and 2 are non-compliant as the sequence was not submitted with the application. In the absence of any additional information provided in the Specification with regards to the specific sequences of SEQ ID No. 1 and 2 as recited in claim 8, SEQ ID No. 1 and 2 is considered to have the same sequence as SEQ ID No. 5 and 6, respectively, as disclosed by Hoffmann *et al.* Furthermore, as evidenced by Ulloa-Aguirre *et al.*, N-glycosylation of human FSH occurs at positions N52 and N78 of the α-subunit, and at positions N7 and N24 of the β-subunit.

As such, it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of M'Timkulu, concerning the conjugation of PEG polymers to biologically active macromolecules through the glycosylations present on those macromolecules, with the teachings of the Kinstler '398 patent, regarding the attachment of PEG polymers to the sialic acid residue of EPO as a means to alter their serum half-life, with the teachings of the Martinez '575 patent, regarding the conjugation of branched, non-antigenic PEG polymers to biologically active molecules such as proteins and peptides as a means to extend their circulating half-life *in vivo*, with the

teachings of Hoffmann *et al.*, regarding the sequence of the α- and β-subunits of FSH from mammalian and *homo sapiens* sources. While the combined teachings of M'Timkulu, the Kinstler '398 patent, and the Martinez '575 patent do not teach the sequence of FSH that is to be modified with a glycoPEG polymer, it would have been *prima facie* obvious for one of ordinary skill in the art to select from among known FSH sequences, such as that disclosed by Hoffmann *et al.*, with the expectation that all known FSH sequences exhibit similar properties. With regards to the exact site of glycoPEGylation, as Ulloa-Aguirre *et al.* teach that N-glycosylation of human FSH is known to occur at only four asparagine sites, namely at positions N52 and N78 of the α-subunit, and at positions N7 and N24 of the β-subunit, one of ordinary skill in the art would reasonably expect that PEGylation would occur only at these four asparagine sites, thereby meeting the instant claim limitations.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).
A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 10 and 23 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12, 18 and 19 of copending U.S. application no. 12/418,530, in view of U.S. Patent No. 6,586,398 B1 to Kinstler *et al.* (hereinafter referred to as the '398 patent; PTO-892, Ref. C).

Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application is drawn to a method of making a composition comprising a first polypeptide conjugate, wherein said first polypeptide conjugate comprises a first number of poly(alkylene oxide) moieties covalently linked to said first polypeptide. The poly(alkylene oxide) moieties are linked to the polypeptide via an O-linked or N-linked glycan residue. Claim 9 indicates that the poly(alkylene oxide) moieties is selected from the group consisting of poly(ethylene glycol) or poly(propylene glycol). Claim 12 indicates that the peptide may be selected from a group that includes follicle stimulating hormone. Claim 19 indicates that the glycosyl linking moiety may be selected from a group that includes sialic acid.

The claims of the instant application are drawn to a follicle stimulating hormone peptide conjugate comprising at least one moiety having the formula as shown in instant claim 1. Claims 3-5 further limit the modifying group present on the conjugate to branched PEG polymers as recited in said claims.

The copending application does not expressly disclose that the site of conjugation of PEG onto the sialic acid residue. The Kinstler '398 patent teaches that water-soluble polymers, such as PEG, can be linked to a hyperglycosylated

erythropoietin analog (NESP) by various methods, one of which involves the mild oxidation of NESP under conditions selected to target the pendant diol of the penultimate glycosyl unit sialic acid for oxidation to an aldehyde (column 5, lines 25-32). The resultant glycoaldehyde is then reacted with the water-soluble polymer, such as a PEG compound.

Thus, based on the teachings of the Kinstler '398 patent, one of ordinary skill in the art would have been motivated to attach PEG to the pendant diol position of the sialic residue of the FSH peptide disclosed in copending U.S. application no. 12/418,530, with the expectation that such a conjugation reaction would result in the desired conjugate.

Thus, the instant claims 1, 10 and 23 are seen to be obvious over claims 1-12, 18 and 19 of copending U.S. application no. 12/418,530, in view of U.S. Patent No. 6,586,398 B1 to Kinstler *et al.*

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim 1 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2 and 12 of copending U.S. application no. 12/152,587, in view of U.S. Patent No. 6,586,398 B1 to Kinstler *et al.* (hereinafter referred to as the '398 patent; PTO-892, Ref. C).

Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application is drawn to a polypeptide conjugate

comprising the structure as shown in formula (I). Claim 2 indicates that the peptide may be follicle stimulating hormone. Claim 12 indicates that the polymeric moiety is poly(ethylene glycol).

The claims of the instant application are drawn to a follicle stimulating hormone peptide conjugate comprising at least one moiety having the formula as shown in instant claim 1. Claims 3-5 further limit the modifying group present on the conjugate to branched PEG polymers as recited in said claims.

The copending application does not expressly disclose that the glycosyl moiety of the peptide for conjugation of the polymeric moiety is a sialic acid residue. The Kinstler '398 patent teaches that water-soluble polymers, such as PEG, can be linked to a hyperglycosylated erythropoietin analog (NESP) by various methods, one of which involves the mild oxidation of NESP under conditions selected to target the pendant diol of the penultimate glycosyl unit sialic acid for oxidation to an aldehyde (column 5, lines 25-32). The resultant glycoaldehyde is then reacted with the water-soluble polymer, such as a PEG compound.

Thus, based on the teachings of the Kinstler '398 patent, one of ordinary skill in the art would have been motivated to attach PEG to the sialic residue of the FSH peptide disclosed in copending U.S. application no. 12/152,587, with the expectation that such a conjugation reaction would result in the desired conjugate.

Thus, the instant claim 1 is seen to be obvious over claims 1, 2 and 12 of copending U.S. application no. 12/152,587, in view of U.S. Patent No. 6,586,398 B1 to Kinstler *et al.*

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim 1 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 10, 16, 19 and 21 of copending U.S. application no. 11/781,885.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application is drawn to a polypeptide conjugate comprising the structure as shown in formula (V). Claim 19 indicates that the peptide may be selected from a group that includes follicle stimulating hormone. Claim 16 indicates that the polymeric moiety is poly(ethylene glycol). Claim 21 indicates that the polymeric moiety is attached via the sugar residue denoted as formula (VII).

The claims of the instant application are drawn to a follicle stimulating hormone peptide conjugate comprising at least one moiety having the formula as shown in instant claim 1. Claims 3-5 further limit the modifying group present on the conjugate to branched PEG polymers as recited in said claims.

Thus, the instant claim 1 is seen to be obvious over claims 10, 16, 19 and 21 of copending U.S. application no. 11/781,885.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim 1 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 13, 20, 23 and 26 of copending U.S. application no. 11/781,900.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application is drawn to a polypeptide conjugate comprising the structure as shown in formula (V). Claim 23 indicates that the peptide may be selected from a group that includes follicle stimulating hormone. Claim 20 indicates that the polymeric moiety is poly(ethylene glycol). Claim 26 indicates that the polymeric moiety is attached via the sugar residue denoted as formula (VII).

The claims of the instant application are drawn to a follicle stimulating hormone peptide conjugate comprising at least one moiety having the formula as shown in instant claim 1. Claims 3-5 further limit the modifying group present on the conjugate to branched PEG polymers as recited in said claims.

Thus, the instant claim 1 is seen to be obvious over claims 13, 20, 23 and 26 of copending U.S. application no. 11/781,900.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1 and 3 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 3, 5, 6, 10, 15, 16, 19, 21 and 22 of copending U.S. application no. 11/781,888.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application is drawn to a generic polypeptide conjugate as defined in claim 1, as well as a polypeptide conjugate comprising the structure as shown in formula (V). Claims 6 and 19 indicate that the peptide may be selected from a group that includes follicle stimulating hormone. Claims 3, 5 and 16 indicate that the polymeric moiety is poly(ethylene glycol) that is linear or branched, with structures as defined in said claims. Claims 5 and 21 indicate that the polymeric moiety is attached via the sugar residue denoted as formulas (III) or (VII).

The claims of the instant application are drawn to a follicle stimulating hormone peptide conjugate comprising at least one moiety having the formula as shown in instant claim 1. Claims 3-5 further limit the modifying group present on the conjugate to branched PEG polymers as recited in said claims.

Thus, the instant claims 1 and 3 are seen to be obvious over claims 1, 3, 5, 6, 10, 15, 16, 19, 21 and 22 of copending U.S. application no. 11/781,888.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim 1 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 27, 32, 38 and 39 of copending U.S. application no. 11/866,969, in view of U.S. Patent No. 6,586,398 B1 to Kinstler *et al.* (hereinafter referred to as the '398 patent; PTO-892, Ref. C).

Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application is drawn to a method of isolating a first polypeptide conjugate comprising a first number of PEG moieties covalently linked to said first polypeptide, from a second polypeptide conjugate comprising a second number of PEG moieties covalently linked to said second polypeptide. Claim 32 indicates that the peptide may be selected from a group that includes follicle stimulating hormone. Claims 38 and 39 indicate that the PEG moiety is attached to the polypeptide via a glycosyl linking group.

The claims of the instant application are drawn to a follicle stimulating hormone peptide conjugate comprising at least one moiety having the formula as shown in instant claim 1. Claims 3-5 further limit the modifying group present on the conjugate to branched PEG polymers as recited in said claims.

The copending application does not expressly disclose that the glycosyl moiety of the peptide for conjugation of the polymeric moiety is a sialic acid residue. The Kinstler '398 patent teaches that water-soluble polymers, such as PEG, can be linked to a hyperglycosylated erythropoietin analog (NESP) by various methods, one of which involves the mild oxidation of NESP under conditions selected to target the pendant diol of the penultimate glycosyl unit sialic acid for oxidation to an aldehyde (column 5, lines 25-32). The resultant glycoaldehyde is then reacted with the water-soluble polymer, such as a PEG compound.

Thus, based on the teachings of the Kinstler '398 patent, one of ordinary skill in the art would have been motivated to attach PEG to the sialic residue of the FSH

peptide disclosed in copending U.S. application no. 11/866,969, with the expectation that such a conjugation reaction would result in the desired conjugate.

Thus, the instant claim 1 is seen to be obvious over claims 27, 32, 38 and 39 of copending U.S. application no. 11/866,969, view of U.S. Patent No. 6,586,398 B1 to Kinstler *et al.*

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1, 3 and 23 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8, 10, 23 and 26-28 of copending U.S. application no. 11/781,896.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application is drawn to a generic polypeptide conjugate as defined in claim 1. Claims 8 and 23 indicate that the peptide may be selected from a group that includes follicle stimulating hormone. Claims 3, 4, 7 and 27 indicate that the polymeric moiety is poly(ethylene glycol) that is linear or branched, with structures as defined in said claims. Claims 7 and 26 indicate that the polymeric moiety is attached via the sugar residue denoted as formulas (III) or (VII).

The claims of the instant application are drawn to a follicle stimulating hormone peptide conjugate comprising at least one moiety having the formula as shown in instant claim 1. Claims 3-5 further limit the modifying group present on the conjugate to branched PEG polymers as recited in said claims.

Thus, the instant claims 1, 3 and 23 are seen to be obvious over claims 1-8, 10, 23 and 26-28 of copending U.S. application no. 11/781,896.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1, 3 and 23 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8, 10, 23 and 26-28 of copending U.S. application no. 11/781,902.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application is drawn to a generic polypeptide conjugate as defined in claim 1. Claims 8 and 23 indicate that the peptide may be selected from a group that includes follicle stimulating hormone. Claims 3, 4, 7 and 27 indicate that the polymeric moiety is poly(ethylene glycol) that is linear or branched, with structures as defined in said claims. Claims 7 and 26 indicate that the polymeric moiety is attached via the sugar residue denoted as formulas (III) or (VII).

The claims of the instant application are drawn to a follicle stimulating hormone peptide conjugate comprising at least one moiety having the formula as shown in instant claim 1. Claims 3-5 further limit the modifying group present on the conjugate to branched PEG polymers as recited in said claims.

Thus, the instant claims 1, 3 and 23 are seen to be obvious over claims 1-8, 10, 23 and 26-28 of copending U.S. application no. 11/781,902.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1 and 23 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 89-136 of copending U.S. application no. 11/714,874.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application is drawn to an O-linked covalent conjugate of a peptide having the formulas as defined in claims 89, 103, 110 or 115. Claim 125 indicates that the peptide may be selected from a group that includes follicle stimulating hormone. Claims 122-124 indicate that the polymeric moiety is poly(ethylene glycol). Claim 112 indicates that the glycosyl linking group is sialic acid. Claim 133 defines the structure of sialic acid modified with the polymeric modifying group PEG.

The claims of the instant application are drawn to a follicle stimulating hormone peptide conjugate comprising at least one moiety having the formula as shown in instant claim 1. Claims 3-5 further limit the modifying group present on the conjugate to branched PEG polymers as recited in said claims.

Thus, the instant claims 1 and 23 are seen to be obvious over claims 89-136 of copending U.S. application no. 11/714,874.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1 and 23 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-43 of U.S. Patent No. 7,473,680 B2.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the patent is drawn to a method of forming a covalent conjugate between a water soluble polymer and a glycosylated or non-glycosylated peptide. Claims 41 and 43 indicate that the peptide may be selected from a group that includes follicle stimulating hormone. Claims 5-8, 21-23 and 42 indicate that the polymeric moiety is poly(ethylene glycol). Claim 42 further indicates that PEG is conjugated to the glycosyl linking group sialic acid at C-5. Claim 133 defines the structure of sialic acid modified with the polymeric modifying group PEG.

The claims of the instant application are drawn to a follicle stimulating hormone peptide conjugate comprising at least one moiety having the formula as shown in instant claim 1. Claims 3-5 further limit the modifying group present on the conjugate to branched PEG polymers as recited in said claims.

Thus, the instant claims 1 and 23 are seen to be anticipated by claims 1-43 of U.S. Patent No. 7,473,680 B2.

Claims 1, 7, 9 and 23 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-120 of U.S. Patent No. 7,416,858 B2.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the patent is drawn to a pharmaceutical composition comprising a pharmaceutically acceptable diluent and a covalent conjugate between PEG and a glycosylated or non-glycosylated peptide, wherein said PEG is conjugated to said peptide via a glycosyl linking group, wherein said glycosyl linking group is interposed between and covalently linked to both said peptide and said PEG. Claims 9, 23 and 40, for example, indicate that the peptide may be selected from a group that includes follicle stimulating hormone. Claim 112 indicates that the modified glycosyl moiety, and the glycosyl moiety linking PEG to the peptide, has the structure as in said claim. PEG is conjugated to the glycosyl linking group sialic acid at C-5. Claim 133 defines the structure of sialic acid modified with the polymeric modifying group PEG.

The claims of the instant application are drawn to a follicle stimulating hormone peptide conjugate comprising at least one moiety having the formula as shown in instant claim 1. Claims 3-5 further limit the modifying group present on the conjugate to branched PEG polymers as recited in said claims. Claim 9 further limits the glycosyl moiety of the peptide.

Thus, the instant claims 1, 7, 9 and 23 are seen to be anticipated by claims 1-120 of U.S. Patent No. 7,416,858 B2.

Claims 1, 7 and 23 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-27 of U.S. Patent No. 7,138,371 B2.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the patent is drawn to a covalent conjugate between PEG and a peptide, wherein said PEG is covalently attached to said peptide at a glycosyl or amino acid residue of said peptide via an intact glycosyl linking group comprising a sialic acid residue covalently linked to said PEG. Claims 14, 19 and 25 indicate that the peptide may be selected from a group that includes follicle stimulating hormone. Claims 11, 17 and 24, for example, indicate at which position PEG is conjugated to sialic acid.

The claims of the instant application are drawn to a follicle stimulating hormone peptide conjugate comprising at least one moiety having the formula as shown in instant claim 1. Claims 3-5 further limit the modifying group present on the conjugate to branched PEG polymers as recited in said claims. Claim 9 further limits the glycosyl moiety of the peptide.

Thus, the instant claims 1, 7 and 23 are seen to be anticipated by claims 1-27 of U.S. Patent No. 7,138,371 B2.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SCARLETT GOON whose telephone number is 571-270-5241. The examiner can normally be reached on Mon - Thu 7:00 am - 4 pm and every other Fri 7:00 am - 12 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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